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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,860	05/21/2007	Takashi Nishimura	3691-0133PUS1	8593

2292 7590 10/07/2011

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
10/07/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/583,860	NISHIMURA ET AL.	
	Examiner	Art Unit	
	SHIN LIN CHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7-12-11 & 9-15-11*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,5-9 and 13-22* is/are pending in the application.

5a) Of the above claim(s) *6,14 and 18-21* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,5,7-9,13,15-17 and 22* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-12-11 has been entered.

Applicant's amendment filed 9-15-11 has been entered. Claim 1 has been amended. Claims 3, 4, 11 and 12 have been canceled. Claims 1, 5-9 and 13-22 are pending. Claims 1, 5, 7-9, 13, 15-17 and 22 and the species WT1 are under consideration.

Claim Objections

2. Claim 7 is objected to because of the following informalities: Claim 7 depends from non-elected claim 6. Amending the claim to depend from only the claim that is under consideration would be remedial. Appropriate correction is required.

3. Claim 15 is objected to because of the following informalities: Claim 15 depends from non-elected claim 14. Amending the claim to depend from only the claim that is under consideration would be remedial. Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 5, 7-9, 13, 15-17 and 22 are rejected under 35 U.S.C. 102(a) as being anticipated by Morgan et al., September 2003 (The Journal of Immunology, Vol. 171, p. 3287-3295).

Claims 1, 5, 7, 8 and 22 are directed to a process of preparing cells for cell therapy comprising inducing helper T1 cells that have a nonspecific antitumor activity from leukocytes isolated from a patient, and imparting antigen specificity to the helper T1 cells by transducing the helper T1 cells with a MHC class I-restricted T cell receptor gene that recognizes a cancer-associated antigen, wherein the helper T1 cells are activated or proliferated. Claim 5 recites the cancer-associated antigen could be gp-100. Claims 7 and 8 specify further purifying the Th1 cells to which antigen specificity has been imparted by using antibody-bearing magnetic beads. Claim 22 specifies the T1 cell receptor gene is isolated from a tumor specific human cytotoxic T cell clone. Claim 9, 13 and 15-17 are directed to a process of preparing cells for cell therapy comprising inducing Th1 cells and Tc1 cells having a nonspecific antitumor activity and imparting antigen specifically to the Th1 cells and Tc1 cells by transducing the Th1 cells and Tc1 cells with a MHC class I-restricted TCR gene that recognizes a cancer-associated antigen, wherein the helper T1 cells are activated or proliferated. Claim 13 recites the cancer-associated antigen could be gp-100. Claims 15 and 16 specify further purifying the Th1 cells and Tc1 cells to which antigen specificity has been imparted by using antibody-bearing magnetic beads. Claim 17 specifies further comprising a step of mixing the separated Th1 cells and Tc1 cells in any given proportion.

Morgan teaches "high efficiency TCR gene transfer into primary human lymphocytes affords avid recognition of melanoma tumor antigen glycoprotein 100" (e.g. title). Morgan isolated DNA fragment encoding alpha- and beta-chain of the TCR from a highly acid anti-gp100 CTL clone, constructed retroviral vectors expressing the alpha- and beta-chain TCR, and transduced primary human lymphocytes with the retroviral vectors. "The biological activity of transduced cells was confirmed by cytokine production following coculture with stimulator cells pulsed with go100 peptides, but not with unrelated peptides. The ability of this anti-gp100 TCR gene to transfer high avidity Ag recognition to engineered lymphocytes was confirmed in comparison with highly avid antimelanoma lymphocytes by the high levels of cytokine production (>200,000 pg/ml IFN-gamma), by recognition of low levels of peptide (<200 pM), and by HLA class I-restricted recognition and lysis of melanoma tumor cell lines. CD4+ T cells engineered with this anti-gp100 TCR gene were Ag reactive, suggesting CD8-independent activity of the expressed TCR" (e.g. abstract). Transduced TCR-engineered peripheral blood lymphocyte cells were cocultured with gp100 peptide-pulsed T2 cells and gated by FACS for CD3+ and CD8+ cells, which were analyzed for the expression of T cell activation marker CD69 and intracellular expression of IFN-gamma. Between 19 and 22% of anti-gp1—TCR-engineered cells were positive for CD69 and IFN-gamma (e.g. p. 3291, right column, 2nd paragraph). Since TCR gene transfer is evenly distributed into CD8 and CD4 cells, bulk population of transduced PBL cells were depleted of CD8 cells by using magnetic beads. The CD4+/CD8- lymphocytes release peptide-specific cytokine at a level of 1800-2245 pg/ml, which is 10-fold higher than the cytokine release from control-engineered cells (e.g. p. 3292, bridging left column and right column). CD4+/CD8- cells are considered helper T1 cells and CD8+/CD3+ cells are considered

Tc1 cells. The gene encoding alpha- and beta-chain TCR from anti-gp100 CTL clone is MHC class I-restricted TCR gene. Melanoma tumor antigen gp100 is a cancer-associated antigen. The TCR-engineered CD4+/CD8- cells are activated and purified. The human peripheral blood lymphocytes are considered mixed separated Th1 cells and Tc1 cells in a given proportion. Thus, the claims are anticipated by Morgan.

6. Claims 1, 5, 7, 9, 13, 15, 17 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Clay et al., 1999 (The Journal of Immunology, Vol. 163, p. 507-513).

Claims 1, 5, 7 and 22 are directed to a process of preparing cells for cell therapy comprising inducing helper T1 cells that have a nonspecific antitumor activity from leukocytes isolated from a patient, and imparting antigen specificity to the helper T1 cells by transducing the helper T1 cells with a MHC class I-restricted T cell receptor gene that recognizes a cancer-associated antigen, wherein the helper T1 cells are activated or proliferated. Claim 5 recites the cancer-associated antigen could be MART. Claim 7 specifies further purifying the Th1 cells to which antigen specificity has been imparted. Claim 22 specifies the T1 cell receptor gene is isolated from a tumor specific human cytotoxic T cell clone. Claim 9, 13, 15 and 17 are directed to a process of preparing cells for cell therapy comprising inducing Th1 cells and Tc1 cells having a nonspecific antitumor activity and imparting antigen specifically to the Th1 cells and Tc1 cells by transducing the Th1 cells and Tc1 cells with a MHC class I-restricted TCR gene that recognizes a cancer-associated antigen, wherein the helper T1 cells are activated or proliferated. Claim 13 recites the cancer-associated antigen could be MART. Claim 15 specifies further purifying the Th1 cells and Tc1 cells to which antigen specificity has been imparted. Claim 17

specifies further comprising a step of mixing the separated Th1 cells and Tc1 cells in any given proportion.

Clay teaches transducing human peripheral blood lymphocytes (PBL) with genes encoding an alphabeta TCR from a MART-1-specific, HLA-A2-restricted human T cell clone, the transduced PBL cultures were MART-1 peptide reactive and most cultures recognized HLA-A2+ melanoma lines. All CD8+ clones specifically secreted IFN-gamma in response to T2 cells pulsed with MART-1(27-35) peptide and 23 of 29 specifically secreted IFN-gamma in response to HLA-A2+ melanoma cell lines. "CD4+ clones specifically secreted IFN-gamma in response to T2 cells pulsed with the MART-1(27-35) peptide. TCR gene transfer to patient PBL can produce CTL with anti-tumor reactivity in vitro and could potentially offer a treatment for patients with metastatic melanoma" (e.g. abstract). Transduced PBL were expanded with anti-CD3 stimulation and cells were tested for reactivity on day 12 in cytokine release assays and peptide-specific/tumor-specific cloids were restimulated and expanded (e.g. p. 508, bridging left and right column). Clones from PBL-65 were CD4+, CD8+ or a mixture of CD4+ and CD8+ T cells, the CD4+ clones secret IFN-gamma when stimulated with T2 cells pulsed with m9-27 peptide but not tumor cells (e.g. p. 510, left column, Table 2). CD4+ cells are considered helper T1 cells and CD8+ cells are considered Tc1 cells. The gene encoding alpha- and beta-chain TCR from MART-1-specific, HLA-A2-restricted human T cell clone is MHC class I-restricted TCR gene. Melanoma tumor antigen MART-1 is a cancer-associated antigen. The TCR-transduced CD4+ and CD8+ cells are activated and purified. The human peripheral blood lymphocytes are considered mixed separated Th1 cells and Tc1 cells in a given proportion. Thus, the claims are anticipated by Clay.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 7-9, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clay et al., 1999 (The Journal of Immunology, Vol. 163, p. 507-513) in view of Bell et al., 2003 (US Patent No. 6,610,542 B1).

Claims 1, 7 and 8 are directed to a process of preparing cells for cell therapy comprising inducing helper T1 cells that have a nonspecific antitumor activity from leukocytes isolated from a patient, and imparting antigen specificity to the helper T1 cells by transducing the helper T1 cells with a MHC class I-restricted T cell receptor gene that recognizes a cancer-associated antigen, wherein the helper T1 cells are activated or proliferated. Claims 7 and 8 specify further purifying the Th1 cells to which antigen specificity has been imparted by using antibody-bearing

magnetic beads. Claim 9, 15 and 16 are directed to a process of preparing cells for cell therapy comprising inducing Th1 cells and Tc1 cells having a nonspecific antitumor activity and imparting antigen specifically to the Th1 cells and Tc1 cells by transducing the Th1 cells and Tc1 cells with a MHC class I-restricted TCR gene that recognizes a cancer-associated antigen, wherein the helper T1 cells are activated or proliferated. Claims 15 and 16 specify further purifying the Th1 cells and Tc1 cells to which antigen specificity has been imparted by using antibody-bearing magnetic beads.

Clay teaches transducing human peripheral blood lymphocytes (PBL) with genes encoding an alphabeta TCR from a MART-1-specific, HLA-A2-restricted human T cell clone, the transduced PBL cultures were MART-1 peptide reactive and most cultures recognized HLA-A2+ melanoma lines. All CD8+ clones specifically secreted IFN-gamma in response to T2 cells pulsed with MART-1(27-35) peptide and 23 of 29 specifically secreted IFN-gamma in response to HLA-A2+ melanoma cell lines. "CD4+ clones specifically secreted IFN-gamma in response to T2 cells pulsed with the MART-1(27-35) peptide. TCR gene transfer to patient PBL can produce CTL with anti-tumor reactivity in vitro and could potentially offer a treatment for patients with metastatic melanoma" (e.g. abstract). Transduced PBL were expanded with anti-CD3 stimulation and cells were tested for reactivity on day 12 in cytokine release assays and peptide-specific/tumor-specific cloids were restimulated and expanded (e.g. p. 508, bridging left and right column). Clones from PBL-65 were CD4+, CD8+ or a mixture of CD4+ and CD8+ T cells, the CD4+ clones secret IFN-gamma when stimulated with T2 cells pulsed with m9-27 peptide but not tumor cells (e.g. p. 510, left column, Table 2). CD4+ cells are considered helper T1 cells and CD8+ cells are considered Tc1 cells. The gene encoding alpha- and beta-chain

TCR from MART-1-specific, HLA-A2-restricted human T cell clone is MHC class I-restricted TCR gene. Melanoma tumor antigen MART-1 is a cancer-associated antigen. The TCR-transduced CD4+ and CD8+ cells are activated and purified.

Clay does not specifically teach using antibody-bearing magnetic beads to purify helper T1 cells.

Bell teaches a method of expanding CD4 and CD8 T cells from HIV infected patients (e.g. abstract). CD4 cells can be purified by using anti-CD4 antibody-coated magnetic beads, and the positively selected CD4 cells are eluted from the beads and cultured in medium (Detailed Description Text (58)).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to use antibody-bearing magnetic beads to purify Th1 T cells because Bell teaches purifying CD4+ cells, which are Th1 cells, from a mixture of cells by using anti-CD4 antibody-coated magnetic beads.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to expand the CD4+ cells as taught by Clay or Bell with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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